Feasibility of Diagnosing Initial Orthostatic Hypotension Using a Continuous Blood Pressure Device in Geriatric Rehabilitation Inpatients: RESORT

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Keywords

Aged · Blood pressure monitors · Initial orthostatic hypotension · Orthostatic · Geriatrics

Abstract

Background: Initial orthostatic hypotension (IOH) is highly prevalent in older adults and may interfere with the ability to regain function after acute hospitalization. IOH assessment requires a non-invasive, beat-to-beat continuous blood pressure device, which is not widely used in geriatric rehabilitation. Our aim was to test the feasibility of diagnosing IOH using a continuous blood pressure device in geriatric rehabilitation inpatients. **Methods:** Geriatric rehabilitation inpatients of the RESORTing Health of Acutely Unwell Adults (RESORT) cohort admitted to a tertiary hospital were randomly selected to undergo continuous blood pressure monitoring (Finapres) for 5 min in the supine position and 3 min of standing or sitting when unable to stand. Interventions to warm hands and adjusting the cuff pressure sizes were attempted if no signal was obtained or an error message occurred. **Results:** Of 37 randomly selected inpatients, 29 {55.2% female; mean age 82.8 (standard deviation [SD]) 6.6 years} agreed to the continuous blood pressure measure-

ment. Successful measurements were achieved in 20 out of 29 inpatients, two after hand warming. Patients with unsuccessful measurements were likely to be older (mean age 87.2 [SD] 4.4 years, $p = 0.03$), have cerebrovascular disease ($p = 0.006$), lower body mass index ($p = 0.012$), and a lower short physical performance battery score ($p = 0.039$). Eight out of 20 patients had IOH. **Conclusion:** The number of unsuccessful continuous blood pressure measurements was high in a population with high IOH prevalence despite multiple interventions to establish a signal. Future research should focus on improving the efficiency of continuous blood pressure devices in hospitalized patients with unsuccessful signals.

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Introduction

Initial orthostatic hypotension (IOH) is a clinical syndrome defined as a transient decrease of ≥ 40 mm Hg systolic blood pressure (SBP) and/or ≥ 20 mm Hg diastolic blood pressure (DBP) within 15 s of active standing [1]. The prevalence of IOH is 27.8% in the older general populations and 35.2% in geriatric outpatients [2] with a high

prevalence of orthostatic intolerance symptoms in older adults, with IOH ranging between 24 and 100% [3]. Unlike classical orthostatic hypotension (COH) which can be detected using a conventional sphygmomanometer [4], the diagnosis of IOH requires non-invasive, beat-to-beat, continuous blood pressure monitoring to evaluate blood pressure changes occurring within 60 s after active standing [4] or passive tilting [1]. These measurements rely on the volume-clamp method [5]. Currently, the clinical use of continuous blood pressure devices in older adults is limited due to its high cost and poor applicability [6]. However, the assessment of haemodynamic responses to postural change is important in older adults due to the association of IOH with hospitalizations, injurious falls, frailty, and mortality [7, 8].

Limited studies have assessed the feasibility of using continuous blood pressure devices like Finapres NOVA to measure IOH in hospitalized older adults [2] due to the more complex application of continuous blood pressure devices than the use of sphygmomanometers [6]. Use of continuous blood pressure devices may be particularly limited by blood circulation impairments in geriatric patients with acute and chronic diseases and subsequent high medication use. Because of this, determining IOH in geriatric rehabilitation patients poses a clinical challenge. However, implementing continuous blood pressure devices in routine clinical care for older adults may help to identify IOH sooner and aid clinicians to minimize the negative outcomes associated with IOH [9].

The aims of this study were to assess the feasibility of diagnosing IOH using continuous blood pressure measurement in geriatric rehabilitation inpatients by establishing the number of successful IOH measurements defined as the presence of a signal with measurable waveforms throughout the last 60 s before postural change and during the 180 s of active stand or sit. Patient characteristics of successful and unsuccessful measurements were compared.

Methods

Study Population and Setting

The REStORing health of acutely unwell adults (RESORT) is an ongoing prospective, longitudinal, observational cohort of subacute geriatric rehabilitation patients at the Royal Melbourne Hospital (Victoria, Australia), assessing their physical, cognitive, and functional status. In a random sample of patients admitted between February 14, 2020, and March 13, 2020, continuous blood pressure measurements were added to the study protocol. Written informed consent was obtained by the patient themselves or a nominated proxy. Patients were excluded if they were receiving

palliative care, transferred to acute care prior to consenting to the study, or incapable of providing informed consent due to delirium or severe dementia without a nominated proxy.

Patient Characteristics

Patients were assessed within 48 h of admission to the geriatric rehabilitation wards by physicians, nurses, physiotherapists, occupational therapists, and dietitians. Information on age, sex, smoking status (current or past smoking), morbidity, and medication were extracted from medical charts. Comorbidity was assessed using the Charlson Comorbidity Index [10] and Cumulative Illness Rating Scale [11]. Cardiovascular disease included any past history of angina, myocardial infarction, cardiac failure, valvular pathology, atrial fibrillation, or other arrhythmias [12]. Cognitive impairment was assessed by physicians and defined as being present if it was recognized on either the Charlson comorbidity index or Cumulative Illness Rating Scale; mild cognitive impairment or dementia mentioned as a diagnosis in the discharge summary; or standardized Mini-Mental State Examination [13] score of <24 points, Rowland Universal Dementia Assessment Scale (RUDAS) [14] score of <23 points, and Montreal Cognitive Assessment [15] score of <26 points. Fall history was defined by self-reported falls in the last 12 months. Physical functioning was assessed by the physiotherapist using the short physical performance battery assessment [16] and functional ambulation classification [17] and by the occupational therapist using the Katz Index of ADL [18] and the Lawton and Brody's instrumental activities of daily living (IADL) scale [19]. The frailty status was assessed using the 9-point Clinical Frailty Scale (CFS) (1 is considered fit and 9 extremely frail [20]). Nutritional status was assessed by the body mass index [21] and malnutrition screening tool [22].

Continuous Blood Pressure Measurement – Experimental Protocol

Continuous blood pressure measurements were performed by a trained staff member using a non-invasive, beat-to-beat blood pressure monitoring device (Finapres NOVA; Finapres Medical Systems, Amsterdam, The Netherlands). A finger cuff was applied to the patient's non-dominant middle phalanx of the third digit and an oscillometric pressure cuff on the ipsilateral upper arm. The patient was asked to maintain the monitored arm across their chest at the heart level, where the height sensor was placed to calibrate and correct for any remaining differences in height between the finger sensor and heart. Patients remained in the supine position for 5 min in silence with the Finometer Physiological function (i.e., the device calibration mechanism to adjust cuff inflation pressure based on the photoplethysmogram) enabled. Manual markings were made on the blood pressure recording once the patient attained a stable supine position and again at the start of transition from supine to standing or sitting position. A cuff size guide ranging from small, medium, or large was used to measure the patient's middle phalanx to determine which cuff size was appropriate. Cuff sizes were readjusted if a cuff error signal was present. If there was no or temporary signal, warming of the hands was performed, firstly, attempted by wearing double-latex gloves on the hand with the finger cuff for 30 min, and if unsuccessful, again attempted with a warm wet towel for another 30 min. Just before standing, Finometer Physiological function was immediately disabled to prevent measurement discontinuities during the measurement. Simultaneously, patients were asked to stand up from the supine position

Fig. 1. Schematic timeline of the experimental protocol.

as quickly as they could and timed with a stopwatch. If patients were not able to stand up, they were asked to assume a sitting position instead. Physical assistance including holding the patient's free arm for support was provided if standing or sitting could not be achieved independently. After postural change, patients remained standing for 3 min in silence, with the monitored arm maintained at the heart level. Immediately following the blood pressure measurement, patients were asked to report whether they experienced symptoms of light-headedness, blurred vision, dizziness, or nausea during postural change. A successful measurement was defined as the presence of a signal with measurable waveforms (i.e., no errors or measurement discontinuities) throughout the last 60 s before postural change and the 180 min of active stand or sit. An unsuccessful measurement was defined as the absence of a signal, poor waveforms, or recurrent error messages during the continuous blood pressure measurement. A schematic timeline of the experimental protocol is demonstrated in Figure 1.

Blood Pressure Data Analysis

Beat-to-beat data of blood pressure and heart rate (HR) were exported to MATLAB (version R2012b; MathWorks, Natick, MA, USA) and filtered using a 5-s moving average filter to attenuate artefacts. Blood pressure parameters obtained to assess IOH included supine SBP and supine DBP, defined as the average blood pressure in the last 60 s before postural change from the supine

position to standing. The relative blood pressure decrease was determined by subtracting the lowest blood pressure at 3 time intervals defined from the start of standing (0–15, 15–60, and 60–180 s) from the supine blood pressure.

Definitions of IOH and COH

IOH was defined as a decrease of ≥ 40 mm Hg SBP and/or ≥ 20 mm Hg DBP within 15 s of active standing or sitting, and COH was defined as a sustained decrease of ≥ 20 mm Hg SBP and/or ≥ 10 mm Hg DBP within 3 min of active standing or sitting [1].

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Advanced Statistics 24.0; IBM Corp, Armonk, NY, USA). Categorical variables are presented as a numerical value (n) with percentages (%), continuous variables with a normal distribution were reported as means and standard deviations (SDs), and skewed distribution (non-Gaussian) data are reported as medians with interquartile ranges. Characteristics between patients with successful and unsuccessful measurements were compared using an unpaired sample t test for continuous data, Mann-Whitney U test for skewed distribution data or the χ^2 test for categorical data. A p value of less than 0.05 was considered statistically significant.

Results

A total of 29 out of 37 randomly selected geriatric rehabilitation inpatients underwent continuous blood pressure measurements. Three patients refused, one patient was unable to provide consent due to a non-English speaking background, 3 due to severe delirium, and 1 had a fistula and lymph node removal on both arms. A flow chart detailing the final cohort is shown in Figure 2. Table 1 shows the participant characteristics for the 29 included patients (mean age was 82.8 years (SD 6.6), 55.2% female) who underwent continuous blood pressure monitoring.

Successful versus Unsuccessful Measurements

During the first attempt of measurements using the continuous blood pressure device, 18 out of 29 patients had a successful measurement. Of the 11 patients who had a poor signal, 9 patients underwent 2 hand warming interventions due to no signal or an error message (i.e., beat detection timeout or LED current problem), which was effective in 2 patients. The remaining 2 patients had a recurrent error message relating to cuff pressure problems. Of the 20 patients with a successful measurement, 15 patients were able to perform an active stand, and 5 patients were able to perform sitting. The total time to complete a successful blood pressure measurement in the first attempt took less than 15 min. The total time to complete a continuous blood pressure measurement in the 9 patients who required multiple attempts due to a poor signal was longer than an hour, with each hand warming intervention lasting 30 min each.

Differences between the Successful and Unsuccessful Measurement Group

Patient's characteristics stratified by a successful ($n = 20$) or unsuccessful ($n = 9$) measurement are given in Table 2. Patients with unsuccessful measurements were older ($p = 0.03$), more likely to have cerebrovascular disease ($p = 0.006$), and had a lower short physical performance battery score ($p = 0.039$) and lower body mass index ($p = 0.012$). There were no statistically significant differences in cognitive impairment or frailty between inpatients with a successful or unsuccessful measurement.

Blood Pressure Characteristics of Inpatients with the Successful Measurement Group

Table 3 presents the blood pressure characteristics of inpatients with successful measurement group. One participant was excluded in the HR analyses due to poor

Table 1. Characteristics of geriatric rehabilitation inpatients at admission

Characteristics	N	Value
Sociodemographic		
Age, mean $\pm$ SD, years	29	83.2 $\pm$ 6.6
Female sex, n	29	16
Current or past smoker, yes, n	27	10
Medical history and medication		
CCI, score (0–37)	29	2 [1–3]
CIRS, score (0–56)	29	11 [8–12]
Cardiovascular disease, yes, n	29	19
Type-2 diabetes mellitus, yes, n	29	8
Cerebrovascular disease, yes, n	29	3
Parkinsonism or Parkinson's disease, yes, n	29	3
Medications number	29	10 [7.25–14.75]
Cognitive impairment, yes, n	29	18
Physical functioning		
Falls in previous 12 months, yes, n	29	22
SPPB, score (0–12)	29	3 [1–6]
FAC, score (0–5)	28	3 [2–3.75]
KADL, median (IQR), score (0–6)	29	2 [1–4]
IADL, median (IQR), score (0–8)	29	1 [1–2.5]
Frailty		
CFS, score (0–9)	29	5 [4–6]
Nutritional status		
BMI, mean $\pm$ SD, kg/m ²	29	28.6 $\pm$ 7.6
MST, score (0–5)	28	0 [0–2]

All values are presented as mean (IQR) unless otherwise stated. IADL, Lawton and Brody's instrumental activities of daily living; KADL, Katz Index of activities of daily living; CCI, Charlson comorbidity index; SPPB, short physical performance battery; FAC, functional ambulation classification; BMI, body mass index; MST, malnutrition screening tool; IQR, interquartile range; CIRS, Cumulative Illness Rating Scale.

quality of data. Mean baseline supine SBP and DBP were 141.2 mm Hg (SD 25.5) and 75.0 mm Hg (SD 14.8), respectively, and HR was 74.0 bpm (SD 11.0). Within the first 15 s, the mean SBP magnitude drop was 36.0 mm Hg (SD 28.7, range 88.1), DBP magnitude drop was 18.3 mm Hg (SD 14.6, range 51.6), and HR increase was 28.3 bpm (22.9–43.4, range 121.8). Representative beat-to-beat waveforms of the blood pressure and HR responses to postural change are shown in Figure 3. IOH was present in 8 out of 20 patients. Of those with IOH, 6 performed active stand, and 2 performed sitting. COH was prevalent in 13 out of 20 patients. Four of the 8 patients with IOH and 7 of the 21 patients without IOH reported at least one or more symptoms of orthostatic intolerance (light-headedness, blurred vision, dizziness, or nausea).

Fig. 2. Flow chart detailing final subsample analysed.

Table 2. Comparison of patient characteristics stratified by successful and unsuccessful measurements

Characteristics	Successful (<i>n</i> = 20)	Unsuccessful (<i>n</i> = 9)	<i>p</i> value
Sociodemographic			
Age, mean $\pm$ SD, years	81.5 $\pm$ 6.8	87.2 $\pm$ 4.4	0.030*
Female sex, <i>n</i>	12	4	0.436
Current or past smoker, yes, <i>n</i>	8	2	0.351
Medical history and medication			
CCI, score (0–37)	6 [4.8–7]	6 [5–7]	0.943
CIRS, score (0–56)	11 [9–12]	11 [6–12]	0.585
Cardiovascular disease, yes, <i>n</i>	5	2	0.872
Type-2 diabetes mellitus, yes, <i>n</i>	7	1	0.183
Cerebrovascular disease, yes, <i>n</i>	0	3	0.006*
Parkinsonism or Parkinson's disease, yes, <i>n</i>	1	2	0.159
Medication number	10 [8–15]	7 [5–10]	0.127
Cognitive impairment, yes, <i>n</i>	11	7	0.242
Physical functioning			
Falls in previous 12 months, yes, <i>n</i>	16	6	0.438
SPPB, score (0–12)	4 [2.8–7]	1 [0–2]	0.039*
FAC, score (0–5)	3 [2.5–4]	3 [1–3]	0.128
KADL, median (IQR), score (0–6)	2 [1–4]	1 [0–2]	0.184
IADL, median (IQR), score (0–8)	1 [1–2]	2 [0–3]	1.000
Frailty			
CFS, score (0–9)	5 [4–6]	6 [4–6]	0.379
Nutritional status			
BMI, mean $\pm$ SD, kg/m ²	30.9 $\pm$ 7.7	23.5 $\pm$ 4.6	0.012*
MST, score (0–5)	0 [0–2]	0 [0–2]	0.549

All values are presented as mean (IQR) unless otherwise stated. IADL, Lawton and Brody's Instrumental Activities of Daily Living; KADL, Katz Index of Activities of Daily Living; CCI, Charlson comorbidity index; SPPB, short physical performance battery; FAC, functional ambulation classification; BMI, body mass index; MST, malnutrition screening tool; IQR, interquartile range; CIRS, Cumulative Illness Rating Scale. * Statistically significant *p* < 0.05.

Discussion

Almost a third of geriatric rehabilitation inpatients had an unsuccessful continuous blood pressure measurement during active standing, impairing the diagnosis of IOH and potentially causing underestimation of IOH prevalence. The poor success rate of continuous blood pressure measurements is unsurprising. High vessel stiffness and endothelial dysfunction [23] are common physiological ageing processes that are prevalent in the geriatric population [24] and can compromise cerebral vasculature [25] and peripheral circulation [26]. Older patients with poor peripheral circulation due to conditions like cold fingers, arthritic fingers, Parkinson's disease (causing rigidity and/ excessive tremor), peripheral vascular disease, or systemic vasculitis [27] can make it challenging to record a reliable continuous blood pressure measurement [28] as it relies on pulsatile unloading of the finger arterial walls [27].

Feasibility of continuous blood pressure measurements in the clinical setting poses additional challenges. The total time to complete a blood pressure measurement using a continuous blood pressure device should take less than 15 min [29]. This includes patient setup and instruction, calibration of finger arterial pressure, 5 min in the supine position, 3 min of active standing or passive sitting, and symptom reporting. A large proportion of our patients had initially a poor signal which meant that the total time to complete a blood pressure measurement extended to over an hour with the addition of the 2 hand warming interventions. Considering the low success rates and the significant time investment required for each blood pressure measurement, implementing routine IOH screening using Finapres may prove challenging in a regular clinical setting.

There are several strategies to optimize the quality of blood pressure recordings, including warming the hand with double-examination gloves and a warm wet towel

Table 3. Blood pressure values and orthostatic intolerance symptoms for inpatients with a successful continuous measurement

Blood pressure characteristics	Value (<i>n</i> = 20)
Supine SBP, mean (SD), mm Hg	141.2 (25.5)
Supine DBP, mean (SD), mm Hg	75.0 (14.8)
Supine HR, mean (SD), bpm	74.0 (11.0)
Prevalence of IOH and COH	
IOH, <i>n</i>	8
IOH in an active stand (<i>n</i> = 15), <i>n</i>	6
IOH in passive sitting (<i>n</i> = 5), <i>n</i>	2
IOH (<i>n</i> = 8) + COH, <i>n</i>	6
COH, <i>n</i>	12
COH in an active stand (<i>n</i> = 15), <i>n</i>	8
COH in passive sitting (<i>n</i> = 5), <i>n</i>	4
COH (<i>n</i> = 12) + IOH, <i>n</i>	6
Orthostatic blood pressure and HR responses in patients with IOH	
SBP drop magnitude, 0–15 s, mean (SD), mm Hg	65.9 (15.8)
DBP drop magnitude, 0–15 s, mean (SD), mm Hg	28.3 (11.7)
HR increase 0–15 s in 1/s, median (IQR)	28.2 [26.3–55.3]
Orthostatic blood pressure and HR responses in patients without IOH	
SBP drop magnitude, 0–15 s, mean (SD), mm Hg	16.0 (13.2)
DBP drop magnitude, 0–15 s, mean (SD), mm Hg	11.7 (12.6)
HR increase 0–15 s in 1/s, median (IQR)	28.3 [19.7–40.7]
Symptoms of orthostatic intolerance in patients with IOH (<i>n</i> = 8)	
Positive symptom(s), <i>n</i>	4
Symptoms of orthostatic intolerance in patients without IOH (<i>n</i> = 12)	
Positive symptoms(s), <i>n</i>	7

IOH = a drop of ≥ 40 mm Hg SBP and/or ≥ 20 mm Hg DBP, within 15 s after active standing or passive sitting. COH = a decrease of ≥ 20 mm Hg SBP and ≥ 10 mm Hg during 15–180 s after active standing or sitting. SBP, drop magnitude = difference between baseline SBP and the lowest measured SBP value in the standing/sitting intervals at 0–15, 15–60, and 60–180 s. Positive symptom(s) is defined as reporting one or more of the following: light-headedness, blurred vision, dizziness, nausea, or pain.

[29]. Although successful in a few patients, this method did not lead to successful measurements in all patients. One study noted improvements in blood pressure measurements when hands were warmed with warm water or a glove filled with warm water [30]. However, this strategy would not be particularly suitable in older patients who are at high risk of falls, especially if unsupervised. Other strategies to consider may include creating multiple cuff sizes to appropriately fit fingers that were too short, overly thin, or arthritic, increasing room temperature to promote cutaneous vasodilation [31], reducing anxiety to reduce peripheral vasoconstriction [32], or attempting to measure continuous blood pressure at an alternative anatomical site. During the blood pressure measurement itself, minimizing external pressures applied to the finger pressure cuff (i.e., pushing off against the bed or supporting oneself during postural change) can reduce

significant artefacts during postural change. A possible solution to decreasing movement artefact or contaminating the blood pressure signal is by supporting the measured arm with a sling [29].

Identifying IOH regardless of the presence of symptoms [33, 34] in geriatric rehabilitation inpatients is clinically important due to the associated high risks of falls, frailty, and syncope [33, 35–38]. This association is due to age-related changes like decreased skeletal muscle strength and cardiorespiratory conditioning which can impair restoration of systemic blood pressure [35, 39, 40]. Currently, continuous blood pressure devices are not readily available in clinical practice due to the high costs and poor applicability [6], leading to underdiagnosis of IOH. Possible strategies to combat IOH, if detected, include rationalizing medications (particularly antihypertensives and psychoactive drugs [41, 42]), standing up

Fig. 3. SBP, DBP, and HR response to active standing in a patient with IOH. The waveforms show a 5-s moving average filter. Time 0: start of postural change. The solid red lines indicate the start and end of postural change. The dotted red line indicates the time 15 s after the end of postural change. The horizontal dotted line indicates the mean value during the 60 s before postural change. The orange, yellow, and purple crosses indicate the minimum value for intervals between 0–15, 15–60, and 60–180 s after the end of postural change, respectively. Green, blue, and red circles indicate the maximum value in intervals between 0–15, 15–60, and 15–180 s after the end of postural change, respectively.

slowly for prolonged activation of skeletal muscle pump [9], contracting lower body muscles to prevent venous pooling [42], and salt supplementation [43]. If IOH is left undetected and thus untreated, this may consequently

lead to poorer clinical outcomes [6]. This study highlights the importance of improving the reliability of continuous blood pressure devices during active stand in geriatric rehabilitation patients to detect IOH [44].

Strengths and Limitations

This is the first study to assess the feasibility of using continuous blood pressure devices to determine initial OH in hospitalized older adults. The strength of this study was the use of a well-defined cohort of older patients admitted to geriatric rehabilitation, providing a clinically relevant study population. There are a few limitations worth noting in our study. No restrictions on hydration status, oral intake, diurnal variation of BP measurement, and medications were placed which may contribute to some measurement variability. One major limitation includes the relatively small sample size which may impact statistical power and validity of this study, possibly overestimating the rate of unsuccessful measurements reported. However, a previous study of similar sample size noted significantly underestimated baroreflex sensitivity with the use of non-invasive blood pressure measurements [45] and may be in keeping with the high unsuccessful rates in our study. Nevertheless, further studies with a larger sample size are recommended to determine the success rates of utilizing non-invasive continuous blood pressure devices to determine IOH in hospitalized older adults with a focus on optimizing the quality of beat-to-beat blood pressure recordings.

Conclusion

The proportion of unsuccessful blood pressure measurements using a continuous blood pressure device was high in geriatric rehabilitation inpatients, who are frequently affected by IOH. This highlights that diagnosing IOH is challenging in this population in a regular clinical setting. Future research should focus on improving the efficiency of continuous blood pressure devices in hospitalized patients with unsuccessful signals.

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Statement of Ethics

The study was approved by Melbourne Health Human Research Ethics Committee (no. 2017.085) and follows national and international ethical guidelines according to the Helsinki Declaration, the National Statement on Ethical Conduct in Human Research (2007), and the Guidelines for Good Clinical Research Practice. Written informed consent was obtained by the patient themselves or a nominated proxy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jennifer Tran contributed to conceptualization, methodology, formal analysis, investigation, writing – original draft, and visualization. Arjen Mol contributed to software, validation, and writing – review and editing. Rebecca K. Iseli contributed to supervision, methodology, and writing – review and editing. Wen Kwang Lim contributed to supervision, methodology, and writing – review and editing. Carel G.M. Meskers contributed to supervision, methodology, and writing – review and editing. Andrea B. Maier contributed to conceptualization, methodology, validation, writing – review and editing, supervision, project administration, and funding acquisition.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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